UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,245	10/09/2001	Joseph Roberts	078728-0104	3976

22428 7590 01/29/2004

FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/972,245	ROBERTS ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *10 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *14-16 and 23-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-13 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

An amendment was received on 11/10/03. Applicant's election with traverse of group I, claims 7-13 and 20-40 is acknowledged.

In a telephone conversation 7/14/04, the Examiner notified Applicant's agent that a typographical error had been made in the restriction, and that group I should have consisted only of claims 7-13 and 20-22. Applicant agreed and elected group I, claims 7-13 and 20-22 with the understanding that claims 1-6 and 17-19 link inventions I and II and that the restriction requirement between these inventions is subject to the non-allowance of the linking claim.

Claims 1-40 remain pending in the Application. Claims 1-13 and 17-22 are under consideration in this Office Action. Linking claims 1-6 and 17-19 are considered to the extent that they embrace the elected invention.

Information Disclosure Statements were received and entered oin 6/5/02 and 1/31/03.

Priority

In the Declaration and Power of Attorney filed 10/9/01, Applicant claims priority to provisional application 60/239,268, filed 10/12/00. However, an application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must

be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See MPEP 2.15. As, no such reference has been submitted within four months of the filing date of this Application, or within sixteen months of the filing date of the provisional application to which priority is claimed, the priority claim cannot be granted. The effective filing date of the instant Application is considered to be 10/9/01.

Drawings

Applicant has submitted informal drawings which are adequate for the purpose of examination, but which may not be acceptable for publication, should allowable subject matter become apparent. Applicant is encouraged to submit formal drawings for review.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-13, and 17-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 5-13, and 17-21 are drawn to the genus of methods of determining modification conditions of a therapeutic agent to prevent host-mediated inactivation of the theraetic agent. The claims do not recite the intended breadth of the term "modification". It is appaernt to one of ordinary skill in the art that a variety of drug modifications are known, both of covalent and non-covalent nature. For example, modification of anionic drugs by complexation with polycations is known in the art, as is covalent derivatization with functonal groups (e.g. alkyl, acyl, phosphate, etc.). However, the specification fails to provide any correlation between the structure of the modifying group, and the intended modifying group, and the intended outcome of the modification, i.e. preotection from host-mediated inactivation.

Adequate written description of a genus may be attained by description of a representative number of species of the genus, either by reduction to practice, drawings, or description of relevant identifying characteristics, e.g. disclosure of a correlation between some structural feature common to the species of the claimed genus and the desired function.The specfication reduces to practice the modification of therapeutic agents by covalent attachment of polyethylene glycol (PEG) moieties, and generally discloses covalent modification with biocompatible polymers, but fails to describe any other modification process directly or by relevant identifying characteristics. Thus one of skill in the art could not conclude that Applicant was in possession of modifying elements that achieve the desired result, other than biocompatible polymers, at the time of the invention. As such, the scope of the claims should be limited to modification with biocompatible polymers.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is indefinite because it is unclear what are the metes and bounds of "extent", so it is unclear what is meant by "modified to the same extent". This term could be interpreted many different ways and it is unclear if Applicant intends any particular interpretation, or all of them. For example, "extent" could mean amount of sites of modification, the size of the modifier, i.e. length of PEG chain, total mass of modifier, total amont of a particular type of modifier, etc.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-7, 9, 10, 12, 13, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez et al ((Med. Pediatr. Oncol. 34(3): 200-205, 2000) in view of Graham et al (Bone Marrow Transplant (21(9): 879-885, 1998), Abshire et al

(Clin. Obs. Interven. Therap. Trials (Blood 96(5): 1709-1715, 9/1/2000), and Francis et al (Int. J. Hematol. 68(1): 1-18, 1998).

Alvarez discloses a comparative study of the effects of pegylated asparaginase relative to those of native asparaginase. Pegylated asparaginase caused toxicity including nausea, vomiting and pancreatitis in greater than half of recipients being treated for ALL. Patients were monitored by sequential serum amylase and lipase determinations.

Alvarez does not teach the comparison of two different types of pegylated asparaginase. Alvarez is silent as to the number of injections of pegylated and native asparaginases.

Graham discloses a clinical trial of pegylated asparaginase in the treatment of acute lymphoblastic leukemia (ALL). Patients received between 1 and 12 doses of pegylated asparaginase. Patients were monitored for relapse throughout the course of treatment. This is considered to amount to an assay of biological activity of the drug. Most of the patients who received the drug developed toxicities which resulted in abbreviated courses of administration. Symptoms included nausea, vomiting, and pancreatitis. See abstract. Evaluations of toxicity are also considered to be measurements of biological activity.

Abshire et al (Clin. Obs. Interven. Therap. Trials (Blood 96(5): 1709-1715, 9/1/2000) taught that pegylated asparaginase showed prolonged half-life and reduced immunogenicity compared to native asparaginase. See paragraph bridging columns 1 and 2 on page 1709.

Francis teaches that pegylation of protein drugs can cause can cause toxicity. See sentence bridging columns 1 and 2 on page 4, and first sentence of paragraph bridging pages 7 and 8. Francis also teaches that bioactivity, stability, immunogenicity, and toxicity may be affected by the way in which a protein drug is pegylated. See abstract, and pages 2-4. Important considerations include the site of attachment of PEG, the degree of modification, the coupling chemistry chosen, the presence or absence of a linker, and generation of harmful co-products. See page 3, column 2, first full paragraph. Francis teaches that the appropriate pegylation method is generally determined empirically by examining a range of different degrees of substitution, as well as different coupling techniques. See page 6, column 1, first full paragraph. The bioactivity retention and other functions of the products may be assessed as a mixture, or individual members of a pegylation series may be assayed individually. See e.g. page 6, first full paragraph of column 1.

At the time the invention was made, pegylation of asparaginase was seen to have both advantages (increased half-life and reduced immunogenicity) and disadvantages (increased toxicity). It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a variety of differently pegylated versions of asparaginase, because Francis suggests that positive attributes of pegylated drugs can be maximized, while minimizing negative attributes, by determining the optimum pegylation conditions. See abstract. It would have been obvious to then compare and test the resulting pegylated forms of asparaginase. It is clear that it was routine in e the art to compare different forms of asparaginase in head to head studies

as taught by Alvarez. It would have been similarly obvious to measure the effects of the drugs after each injection, as patients undergoing treatment for ALL, such as those in the Graham and Alvarez studies, are continuously monitored for disease progress. Claim 5 is included in this rejection because in light of the teachings of Francis, the extent of pegylation is a result-effective variable that is routinely optimized by those of skill in the art. See page 3, column 2, first full paragraph. Claim 6 is included in this rejection because the selection of different coupling chemistries is part of the optimization process suggested by Francis, and different chemistries result in different modifying agents. For example, in the TMPEG method discussed at page 5, the PEG is linked to the polypeptide directly without any linker, whereas other chemistries may cause the introduction of immunogenic groups (see e.g. page 4, column 1, lines 1-10 of first full paragraph. Claim 11 is included in this rejection because

Thus the invention as a whole was prima facie obvious.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez, Graham, Abshire, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, and 17 above, and further in view of Petersen et al (US Patent 6,531,122)

The teachings of Alvarez, Graham, Abshire, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases. Francis also teaches that one reaction chemistry known in the art for PEG modification utilizes a cyanuric chloride linker. See page 4, lines 5-9 of first full paragraph.

These references do not teach SBA-, SC-, and ALD-PEGs.

Petersen teaches that SBA-, SC-, and ALD-PEGs, as well as a variety of other types of modified PEGs, including those with a cyanuric chloride linker, may be used interchangeably to modify polypeptide drugs. See paragraph bridging pages 24 and 25; column 25, first full paragraph, especially, lines 12, 27, 28, and 30; and column 26, lines 36-42.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify asparaginase with any of SBA-, SC-, and ALD-PEGs, because these derivatives were well known equivalents in the prior art. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Thus the invention as a whole was prima facie obvious.

Claims 8, 11, and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez, Graham, Abshire, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, and 17 above, and further in view of Roberts et al (J. Gen. Virol. 72:299-305,1991).

The teachings of Alvarez, Graham, Abshire, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references do not teach an enzyme used to treat viral infection, used to reduce glutamine levels, or asparaginase glutaminase from Pseudomonas.

Roberts teaches that glutaminase asparaginase from Pseudomonas can be used to treat retroviral disease by repeated administration, and that pegylation of the enzyme increases its half-life several fold. See abstract, and page 304, penultimate sentence of column 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Pseudomonas asparaginase glutaminase by. One would have been motivated to do so in order to increase its half-life in vivo and to decrease its immunogenicity, as taught by both Roberts and Francis. It would have been similarly obvious to optimize the pegylation conditions as taught by Francis. In doing so it would have been obvious to deliver differently pegylated forms of the enzyme in vivo over the course of treatment taught by Roberts. It would have been obvious to monitor the progress of the disease over the course of treatment in view of the teachings of Alvarez and Graham, who show that this is routine in the art.

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez, Graham, Abshire, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, and 17 above, and further in view of Bollin et al (US Patent 4,678,812, issued 7/7/87).

The teachings of Alvarez, Graham, Abshire, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references do not teach adding an excipient tat protects asparaginase during lyophilization.

Bollin teaches that proteins can be stabilized by lyophilization and that saccharides are useful in stabilizing asparaginase during lyophilization.

It would have been obvious to one of ordinary skill in the art to add saccharides to the pegylated asparaginases developed by the methods described above, for the purpose of stabilizing them during lyophilization. One would have been motivated to do so because Bollin teaches that proteins may be stabilized by lypohilization, and that asparaginase in particular is stabilized by addition of saccharides during lyophilization.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at 703-306-3217 before 2/22/04, and at 571-272-0811 after 2/22/04. The official central fax number is 703-872-9306 until further notice. Inquiries of a general nature or relating to the status of the application should

be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.